REMARKS

I. Status of the Claims

Claims 1-3, 6-15 and 18-25 are pending. Claims 4, 5, 15, 16, 17, and 26-62 were previously canceled without prejudice or disclaimer. Applicants reserve the right to file one or more continuing applications to any canceled subject matter.

Claim 1 is amended to recite a method for monitoring the *therapeutic* effect of a therapeutic composition on cancer in a mammal and, by performing the recited steps, determining whether the therapeutic composition has a *therapeutic* effect on the cancer.

These amendments introduce no new subject matter and they furthermore place the claims in condition for allowance. Thus, Applicants respectfully request entry of these amendments.

II. Rejection under 35 U.S.C. § 112

Claims 1-3, 6-14, and 18-25 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. Office Action at page 2. The Office characterizes Applicants' claimed invention as being "broadly drawn to methods for monitoring every effect of a therapeutic composition on any cancer in a mammal" where the observation that PAK4 phosphorylation levels decrease after administration of a therapeutic composition "indicates that the therapeutic composition has every type of therapeutic effect on cancer in said mammal." *Id.*

According to the Office, a particular disease state "must be identified in some way with phosphorylated PAK4" and the "essential element of the validation of an early detection marker is the ability to test the marker on clinical material from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease." *Id.* at bottom of page 5 (emphasis in original). If these criteria are not met then "the level of unpredictability for using a marker, such as PAK4 phosphorylation on Ser-474, as an indicator of any particular disease state, or therapeutic effect, is quite high." *Id.* at page 6. That is, the skilled person would have had "to provide extensive experimentation to demonstrate such an association." *Id.*

Applicants respectfully disagree but have amended the claims to reflect (a) that the effect that the recited therapeutic composition has on the cancer in the mammal is a "*therapeutic* effect"; and (b) that the mammal that has cancer is characterized by having "an

elevated level of phosphorylated PAK4," as compared to a mammal that does not have the cancer.

These amendments therefore clarify that the claimed method is to a method for monitoring the therapeutic effect of the composition. Furthermore, the amendment clarifies that the claims do not accommodate "contradictory methods" (Office Action at page 3), but rather that the mammal with cancer exhibits elevated levels of PAK4 phosphorylation, which means a successful "therapeutic effect" of the claimed composition is to decrease PAK4 phosphorylation levels because, in the words of claim 1: "a lower level of PAK4 phosphorylation on ser-474 in the subsequent biopsy compared to the first biopsy indicates that the therapeutic composition has a therapeutic effect on the cancer." Thus, a therapeutic effect of the claimed composition is to lower PAK4 phosphorylation in the cancer-afflicted mammal.

Applicants reiterate that their observation that the level of PAK4 phosphorylation (on ser-474) decreases when a particular therapeutic composition is administered to an individual who has colon cancer, is ***exemplary*** of phosphorylation changes that can be measured in other types of cancers, not only colon cancer. See Example 5 of the application. PAK4 is a kinase that is frequently *overexpressed* in human tumor cell lines of various tissue origins. Please see paragraph 4 of the published application version of the pending case, U.S. 20050054017 ("PAK4 is strongly implicated in oncogenic transformation and suggests that PAK4 activity is required for Ras-driven, anchorage-independent growth"). Since PAK4 is an effector for Cdc42, it is most likely associated with chemotaxis, cell adhesion, inflammatory responses, and innate immunological activities. See paragraph 7 of the published application. For instance, there is evidence implicating PAK kinases in oncogenic Ras-driven, anchorage-independent growth and in the regulation of cell survival. *Id.* But no-one in the prior art had thought it useful to use phosphorylated PAK4 as a biomarker for tumorogenesis in biopsy samples obtained from diseased and healthy mammals. Indeed, Applicants stated in their specification that:

> ...there is no suggestion in the prior art to use phosphorylated PAK4 as a biomarker for tumorogenesis in biopsy samples obtained from diseased and healthy mammals. Similarly, there is no suggestion for using PAK4 phosphospecific antibodies to determine the effect of a therapeutic composition upon a mammal undergoing treatment. Likewise, the art is silent on using PAK4 phosphorylation screening assays to identify compounds that are useful as PAK activity modulators. There also is no teaching in the prior art for detecting and comparing levels of PAK phosphorylation as a means of identifying subsets of

> a given population that are amenable to treatment with PAK activity modulators.

Paragraph [0008].

In light of this, Applicants had provided exemplary results of the usefulness of the claimed method for monitoring the effect of a therapeutic composition on cancer in a mammal, where they had correlated a decrease in ser-474 phosphorylation levels in colon cancer biopsies after treatment with the therapeutic composition. The effect of this, and other therapeutic compositions, can be ascertained in the same way for the cancers listed in Table 1 of Example 4. See also Example 5 and Applicants' conclusion that a level of phosphorylated PAK4 that is above normal in a certain tissue is a useful biomarker for determining the integrity and status of the cells in the tissue:

> The data for the phosphospecific antibody (#108) in colon carcinomas is ***especially*** informative (6 out of 6 patients showed marked perinuclear staining in tumor and not distal benign tissue; note that staining was detected using vector red substrate, which gives a fuchsia/red-colored deposit. ***This result strongly suggests that PAK4 is specifically active in the colon tumor cells and not in benign colon tissue*** from the same patient. Staining of phosphorylated PAK4 was also observed in ***renal cell carcinoma***, ***lung adenocarcinoma***, ***prostatic adenocarcinoma***, ***intraductal breast adenocarcinoma***, and ***ovarian adenocarcinoma*** . . . **Accordingly, a level of phosphorylated PAK4 that is above normal in a certain tissue is a useful biomarker for determining the integrity and status of the cells in the tissue**

Emphasis added; paragraphs [0080] and [0084]

Applicants' specification teaches the skilled artisan that PAK4 phosphorylation levels can be correlated with cancer, and that it is desirable to produce antibodies which recognize specific phosphorylation states of PAK4 and which distinguish between two samples from a patient. The skilled person learned from Applicants' specification and technical guidance provided therein that phosphospecific antibodies can be used to monitor and determine the effectiveness of a candidate anti-cancer drug in modulating the phosphorylation state of PAK4. This understanding was bolstered by Applicants' Examples which taught the skilled person that several carcinomas – (1) renal cell carcinoma, (2) lung adenocarcinoma, (3) prostatic adenocarcinoma, (4) intraductal breast adenocarcinoma, (4) ovarian adenocarcinoma, and (5) colon carcinoma – exhibited elevated PAK4 phosphorylation levels compared to the non-cancerous, benign state of those particular tissues and organs. The skilled artisan therefore learned from Applicants' specification that a level of phosphorylated

PAK4 that is above normal in a certain tissue is a useful biomarker for determining the integrity and status of the cells in the tissue; and, furthermore, would have understood that the effectiveness of a therapeutic composition to lower phosphorylation levels in individuals with colon cancer was simply *exemplary*. All in all, after reading Applicants' specification, the skilled artisan became equipped with both the knowledge and methodological know-how for making and using the claimed inventive method.

For these reasons, therefore, Applicants assert the claimed invention is enabled for a method of monitoring the therapeutic effect of a therapeutic composition on cancer in a mammal by measuring the phosphorylation state of PAK4/ser-474 before and after administration of the composition to the individual, where the mammal has an elevated level of PAK4 phosphorylation. Applicants therefore respectfully request withdrawal of this rejection.

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CONCLUSION

Applicants believe that this case is in condition for allowance and invite the Examiner to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date April 9, 2008 By V. J. Mohan-Ram

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.